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**RESEARCH ARTICLE**

# THALASSEMIA AND IMMUNE SYSTEM DYSFUNCTION-REVIEW ARTICLE

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**ABSTRACT**

Thalassemia major (TM) patients present with severe hemolytic anemia and multiple organs impairment. TM have an increased risk for serious infections, due to that a basic defect in the host defense and this may be related to the iron overload, chronic immune-stimulation by repeated blood transfusions, splenectomy and immune deficiency. changing in lymphocyte subsets include a greater number and activity of suppressor T cells (CD-8),reduced proliferative capacity and a number and level of activity of helper T- Cells (CD-4) leading to decreased CD4/CD8 ratio, as well as defective activity of natural killer (NK) cells. High immune globulins were reported and B-lymphocytes were found to be increased, activated with impaired differentiation, impairment of immunoglobulin secretion accompanied by increased levels of IgG, IgM and IgA. Neutrophils and macrophages are associated with defective chemo taxis and phagocytosis.

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## INTRODUCTION

Thalassemia is an autosomal recessive disease, the most common genetic disorder in worldwide, especially in Mediterranean, caused by mutations of the genes encoding for the globin chains on the chromosome 11 (quantitative defect in globins' chain synthesis) (1). Thalassemia major (TM) patients presents with severe hemolytic anemia from the first year of life and multiple organs impairment that in most homozygous cases, is quite severe and fatal unless repeated blood transfusions are commenced early (2). TM have an increased risk for serious infections, suggesting that a basic defect in the host defense is present and this may be related to the iron overload, chronic immune-stimulation by repeated blood transfusions, splenectomy and immune deficiency. Effects of iron overload include decreased antibody-mediated and mitogen stimulated phagocytosis by monocytes and macrophages , alterations in T-lymphocyte subsets and modification of lymphocyte distribution in different compartments of the immune system(3,4).Infections are a frequent complication of thalassemia (12-13%) and hemoglobinopathies and they can be fatal. Beta-thalassemia major have an increased risk for systemic infections, suggesting that a basic defect in the host defence is present. There are various causes of infection including blood transfusion, splenectomy, iron overload in the body, and aberration of function in immunity system. Infections were the first or second cause of death(after heart failure) in thalessemia and hepatic disease is the third most common cause of death (5-6) .Immune defects in Thalassemia ,recently the immunological abnormalities observed in Thalassemia patients (2,7-8).The immune alterations concern both the innate and the adaptive immune systems (quantitative and functional).Neutrophil chemo taxis, specific antibody response, cell-mediated immunity have been reported to be defective in TM. Immune deficiencies have been suggested as a precipitating factor for the fourth most common cause of death in beta-thalassemia, i.e.malegnancies. Of course severe anemia, itself, is a risk factor for bacterial infections in Thalassemia, predominantly pneumonia (9). Some studies have revealed a decreased activity of T and B lymphocytes, neutropheil , macrophages and complements(10). Some studies have revealed an increased activity of B-lymphocytes (11) and other studies reported normal levels.

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## CATEGORIES

### T-lymphocytes

More specifically, the change in lymphocyte subsets include a greater number and activity of suppressor T cells (CD-8),reduced proliferative capacity and a number and level of activity of helper T- Cells (CD-4)leading to decreased CD4/CD8 ratios, as well as. defective activity of natural killer(NK)cells(10-11,13-14).patients with thalassemia showed significantly increased absolute lymphocyte counts compared to the control group(15).these patients have a

significant increase in the levels of CD3 and CD4 cells compared to the control group. Plasma level of transforming growth factor –β(TGF-β) was higher in thalassmia patients(16). Overproduction of TNF-α and neopterin in splenectomized patients may be related to poor antigen filtration, which results in enhanced inflammatory and cell-mediated immune response to the infused foreign antigens.

**B- Lymphocytes**

Immunoglobulin levels were extensively studied in TM, but conflicting results were described. Besides normal immunoglobulin concentrations (3, 17), increased levels of IgG and / or IgM (10), increased levels of IgA alone (18) were demonstrated in non-splenectomized as well as splenectomized patients. High immune globulins were reported and B- lymphocytes were found to be increased, activated with impaired differentiation (10,13-14, ),impairment of immunoglobulin secretion accompanied by increased levels of IgG , IgM and IgA(10,19-20) but in our study, there were no significant changes in IgG,IgM, IgE, ASO and isohemaglutinin titer compaired to the control ,except IgA which was higher in the TM patients (A).Of course, we showed lower IgM and higher IgA. IgG levels in splenectomised patients and lower ASO with IgM associated higher IgA and IgG levels in diabetic TM patient (7).kiani –Amin reported no any defect in the humeral immune system(IgG and IgM) in all TM patients but the mean serum level of IgA in the non-splenectomized patients under five years old and also in the splenectomized patients above twenty years old were increased(21).Amin study showed that thalassemia patients showed much more increase in serum immunoglobulin levels as they get older (20).selective deficiency of one of the IgG subclasses increases susceptibility to recurrent pyogenic infctions(22).Vergin et al demonstrate that in TM patients , no abnormality in humoral immunological parameters could be detected(23). However, in the majority of the studies, after splenectomy,a further increase of IgG and IgA levels and decrease in IgM levels were observed(18). Speer has found no difference in immunoglobulin levels between nonsplenectomized and splenectomized children (3). study in the Greece reported that levels of IgG and IgA were normal but the IgM level was low after splenectomy (24).

**Neutrophils,Macrophages and Complement**

Neutrophils and macrophages are associated with defective chemo taxis and phagocytosis (18,25).Our study that neutrophil activity in TM patients was significantly lower compared to the normal contract group, especially in young patients (2).suppressed functioning of the complement system (classic or alternative),with reduced levels of $C_3$ and $C_4$, has also been observed (10,20).These defects have been attributed both to the disease itself and the applied therapeutic interventions (10).The same vergin et al study(23),Our Study Showed that there were no significant differences on the level of $C_3$,$C_4$,CH50 between two groups (TM and healthy groups) but there was significant lower levels of $C_4$ and $CH_50$ in TM patients with ferritin level above 3000ng/dl(7). Seitanidis et al have also found normal $C_3$ levels in patients with TM and have reported that the increased susceptibility to infection in these patients was not related to the complement system (26). Neopterin, a catabolic product of guanosine triphosphate is synthesized by monocytes/macrophages upon stimulation with IFN-γ and serves as a marker of cellular immune system activation (27). TNF-α could be increase or decrease in the thalassemia patients (28, 29).

**PATHOGENES**

**T lymphocytes**

Iron excess may tip the immune balance unfavorably to allow increased growth rates of infections organisms (30).iron plays an important role in regulating the expression of T-lymphocyte cell surface markers influencing the expansion of different T-cell subsets and perhaps affecting immune cell functions(30). Intensive chelation therapy by desferrioxamine has been shown to improve some of immune deficiency (31). The low zinc levels in thalassemia patients have been associated with alterations of lymphocyte subsets and thymulin deficiency (32). In asplenia or functional hyposplenia, antibody production in responses to new antigens, mediated by CD4 function is impaired (33). Also, many substances (Opsonins, Properdin, Tufssin) which are reduced in asplenic organisms (34).Multiple transfusions have been associated with autoimmune hemolysis and T-lymphocyte changes.Splenectomy has also been correlated with immune system modifications. These include quantitative lymphocyte change, though without any functional impairment (12). The finding of increased T-cell counts in splenectomized patients may be related to enhanced immune response to the infused foreign antigens, which are not effectively filtered. Gharagozloo et al showed increased absolute counts and percentages of $CD3^+$ $DR^+$, $CD3^+$ $CD25^+$ and $CD3^+$ $CD71^+$ cells in TM (29) , suggesting the presence of a chronic immunological stimulation due to multiple blood transfusion. Also this study showed significant reduction of IL-2, IFN-γ and IL-4 production by activated lymphocytes from patients with TM (29) but Salasa et al showed that blood mononuclear cells from thalassemia patients produced more IFN-γ than control group (35).

**B-lymphocytes**

The mechanisms of such changes in the immunoglobulin were explained, according to hypothesis including iron overload on skin (stimulation of IgA production as a mucocutaneous antibody (3, 11, 29) and repeated exposure to antigens due to repeated transfusions and infections (stimulation of IgM,IgG and IgE production) (36).Of course, as mentioned in our study, decreased level of IgM in TM patients with DM which may indicate impairment of immune system to DM(23). it seems that differing immunoglobulin serum levels in TM could be due to heterogeneity of different studies in aspects including age groups, race, socioeconomic status, nutrition and defference in the care provided for the patient to control anemia and varied measures of ferritin , ignorance of the patient`s simultaneous affliction with hepatitis C and the failure to divide them into two groups of splenectomized and not splenectomized patients. Repetitive transfusions lead to continuous allo-antigenic stimulation and therefore disturbance of the immune balance. Multiple transfusions have been associated with autoimmune hemolysis and B-lymphocyte changes. Zinc is an immune regulator and the low

zinc levels in thalassemia have been associated with alterations of lymphocyte subsets and thymulin deficiency. The latter is corrected after zinc supplementation (32).The increase in circulating CD19 cells observed after splenectomy may result in marked persistence of B cell in the circulation of patients, since the spleen is a major site of B cell differentiation.

**Neutrophils and Macrophages**

In TM, based on in effective erythropoiesis, increased phagocyte activity very likely reduces the capacity of the phagocytic system to defend against microorganisms (37, 38). The pattern of recognition receptors (PRR) are overwhelmed, chemo taxis is also impaired. Regarding polymorphonuclear neutrophils, the impaired phagocytosis activity observed in iron overload results from the deleterious effect of ferritin-associated iron and intensive chelation therapy has been shown to improve some of these symptoms (31).In TM anti-ferritin antibodies leads to the production of circulating immune complexes (30). Multiple transfusions have been associated with autoimmune hemolysis and modification of monocyte and macrophage functions (19,25).

**Infections**

Encapsulated pathogens, streptococcus pneumonia, hemophilus influenza type B, Escherichia coli, Neisseria meningitis are the most fearsome (39). For prevention of infections, particular interest for clinical practice, the optimal timing of vaccine administration, the duration of penicillin prophylaxis and the role of partial splenectomy. Splenectomized and hyposplenic patients receive routine vaccination, both live attenuated and killed vaccines (40). But they should also be immunized against streptococcus pneumonia, H.influenza type b and Neisseria meningitides (41).

**Conclusion**

Immune defects in thalassemia patients involve multiple components of the immune system. Infectious complications constitute an important part of the clinical spectrum of beta-thalassemia.Although, additional studies are required to establish more clearly the etiology, pathogenesis and the clinical significance of the suspected precipitating mechanisms.

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